(FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 14:27:04 ON 11 FEB 2004)

DEL HIS

L1 390576 S FIBROBLAST?
L2 21866 S L1 AND (EXTRACELLULAR MATRIX)
L3 12393 S L2 AND (COLLAGEN OR DECORIN OR FIBRONECTIN OR TENASCIN OR GL
L4 2594 S L3 AND SKIN
L5 146 S L4 AND (TRANSPLANT? OR GRAFT OR BIOENGINE?)
L6 95 DUP REM L5 (51 DUPLICATES REMOVED)
L7 95 FOCUS L6 1-
L8 55 S L7 AND PY<=1999
L9 55 SORT L8 PY
E MURPHY MICHAEL?/AU
E MURPHY MICHAEL/AU
L10 103 S E28
L11 8 S L10 AND L1
L12 6 DUP REM L11 (2 DUPLICATES REMOVED)
L13 6 SORT L12 PY
E RONFARD VINCENT?/AU
L14 9 S E2
L15 13 S E1
L16 0 S L14 AND L15
L17 22 S L14 OR L15
L18 15 DUP REM L17 (7 DUPLICATES REMOVED)
L19 5 S L18 AND L1

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L19 ANSWER 1 OF 5 MEDLINE on STN
AN 2003072369 MEDLINE
TI Long-term remodeling of a bilayered living human skin equivalent (Apligraf) grafted onto nude mice: immunolocalization of human cells and characterization of extracellular matrix.
SO WOUND REPAIR AND REGENERATION, (2003 Jan-Feb) 11 (1) 35-45.
Journal code: 9310939. ISSN: 1067-1927.
AU Guerret Sylviane; Govignon Emmanuel; Hartmann Daniel J; **Ronfard Vincent**
AB Type I collagen is a clinically approved biomaterial largely used in tissue engineering. It acts as a regenerative template in which the implanted collagen is progressively degraded and replaced by new cell-synthesized tissue. Apligraf, a bioengineered living skin, is composed of a bovine collagen lattice containing living human **fibroblasts** overlaid with a fully differentiated epithelium made of human keratinocytes. To investigate its progressive remodeling, athymic mice were grafted and the cellular and the extracellular matrix components were studied from 0 to 365 days after grafting. Biopsies were analyzed using immunohistochemistry with species-specific antibodies and electron microscopy techniques. We observed that this bioengineered tissue provided living and bioactive cells to the wound site up to 1 year after grafting. The graft was rapidly incorporated within the host tissue and the bovine collagen present in the graft was progressively replaced by human and mouse collagens. A normal healing process was observed, i.e., type III collagen appeared transiently with type I collagen, the major collagen isoform present at later stages. New molecules, such as elastin, were produced by the living human cells contained within the graft. This animal model combined with species-specific immunohistochemistry tools is thus very useful for studying long-term tissue remodeling of bioengineered living tissues.

L19 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:171741 CAPLUS
DN 136:205388
TI Methods and compositions for tissue regeneration
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
IN Baetge, Edward E.; Hunziker, Thomas; **Ronfard, Vincent**
AB The present invention provides the use and composition of matter of angiogenic or other growth factors expressed by combining various types and stages of differentiation of allogeneic human cell strains or lines in

unencapsulated pastes (mixed with or applied to extracellular matrix material or synthetic biocompatible substances) to be temporarily applied to wounds or defects in the skin or other tissues for the restoration of blood supplying connective tissue to enable organ-specific cells to reestablish organ integrity as well as to inhibit excessive scar formation.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002017980	A2	20020307	WO 2001-US27104	20010831
	WO 2002017980	A3	20020530		
	WO 2002017980	C2	20030320		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US	2002048563	A1	20020425	US 2001-943114	20010830
US	6673603	B2	20040106		
AU	2001086952	A5	20020313	AU 2001-86952	20010831
EP	1326654	A2	20030716	EP 2001-966441	20010831

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

L19 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:152814 CAPLUS
TI Skin care compositions and treatments
SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2
IN **Ronfard, Vincent**; Tuck, Alan W.; Wilkins, Leon M.
AB The invention is directed to compns. containing growth agents synthesized from cultured cells from skin. Skin cells such as keratinocytes and dermal **fibroblasts** are cultured in vitro in cell medium and in the course of culture the cultured cells synthesize and secrete agents into the cell medium. The medium containing agents are collected and incorporated into pharmaceutical or cosmetic prepns. to treat an individual. The preparation is applied and has a rejuvenating effect on the cells and tissue.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001014527	A1	20010301	WO 2000-US23178	20000823

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

L19 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:351643 CAPLUS
DN 132:331698
TI Bioengineered tissue constructs and methods for producing and using them
SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2
IN Murphy, Michael P.; **Ronfard, Vincent**
AB Cultured tissue constructs comprising cultured cells and endogenously produced extracellular matrix components without the requirement of exogenous matrix components or network support or scaffold members. Some tissue constructs of the invention are comprised of multiple cell layers or more than one cell type. The tissue constructs of the invention have morphol. features and functions similar to tissues and their strength makes them easily handleable. Preferred cultured tissue constructs of the invention are prepared in defined media, i.e., without the addition of chemical

undefined components.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000029553	A1	20000525	WO 1999-US27505	19991119
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1131410	A1	20010912	EP 1999-962807	19991119
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	BR 9915476	A	20020102	BR 1999-15476	19991119
	JP 2002530069	T2	20020917	JP 2000-582537	19991119
	US 2002172705	A1	20021121	US 2000-523809	20000313

L9 ANSWER 44 OF 55 MEDLINE on STN
AN 1998207044 MEDLINE
TI Analysis of matrix protein components of the dermis-like structure formed in a long-term culture of human **fibroblasts**: type VI **collagen** is a major component.
SO JOURNAL OF BIOCHEMISTRY, **(1998 Apr)** 123 (4) 587-95.
Journal code: 0376600. ISSN: 0021-924X.
AU Hazeki N; Yamato M; Imamura Y; Sasaki T; Nakazato K; Yamamoto K; Konomi H; Hayashi T
AB Formation of a dermis-like structure by a long-term culture of **fibroblasts** in the presence of ascorbic acid is a potential model for tissue organization or wound healing, and has its practical use as a **skin graft**. In the present study, solubilization of the dermis-like structure without pepsin treatment was attempted for analysis of pepsin-labile matrix components that might be involved in the formation of the dermis-like structure, as well as quantification of mutated type I **collagen** that could be susceptible to pepsin. The whole dermis-like structure was dissolved in a Tris buffer containing SDS and urea at 80 degreesC. Analysis of the extract by SDS-PAGE revealed several protein bands that were not found in the pepsin-treated extract. Among them, the polypeptide band migrating at 140k under reducing condition showed a similar intensity of protein staining to the alpha2(I) chain band. The N-terminal amino acid sequences of cyanogen bromide peptides derived from the 140k polypeptide band as well as the amino acid composition of the band suggested that the band essentially consisted of alpha1(VI) and alpha2(VI) chains. The results demonstrated that the type VI **collagen** was a major component, being a comparable in amount to type I **collagen**, in the dermis-like structure.

L9 ANSWER 43 OF 55 MEDLINE on STN
AN 1998281608 MEDLINE
TI Organized **skin** structure is regenerated in vivo from **collagen**-GAG matrices seeded with autologous keratinocytes.
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1998 Jun)** 110 (6) 908-16. Journal code: 0426720. ISSN: 0022-202X.
AU Compton C C; Butler C E; Yannas I V; Warland G; Orgill D P
AB A well-characterized **collagen-glycosaminoglycan** matrix (CGM) that has been shown to function as a dermal analog was seeded with freshly disaggregated autologous keratinocytes and applied to full-thickness wounds in a porcine model. CGM were impregnated with 50,000 keratinocytes per cm2, a seeding density that produces a confluent epidermis within 19 d post-grafting and affords a 60-fold surface expansion of the donor epidermis. In this study, the temporal sequence of events in epidermal and neodermal formation was analyzed histopathologically and immunohistochemically from 4 to 35 d post-grafting. The epidermis was observed to form from clonal growth of individual keratinocytes into epithelial cords and islands that gradually enlarged, coalesced, differentiated to form large horn cysts, and finally reorganized at the **graft** surface to form a fully differentiated, normally oriented epidermis with rete ridges. Simultaneously, a neodermis formed from migration of endothelial cells, **fibroblasts**, and macrophages into the CGM from the underlying wound bed, resulting in formation of blood vessels, the production of abundant **extracellular matrix**, and the degradation of the CGM fibers, respectively. Gradually, the stromal cellularity of the CGM decreased and **collagen** deposition and remodeling increased to form a neodermal connective tissue matrix beneath the newly formed epidermis. Complete dissolution of the CGM occurred, partly as a result of degradation by an ongoing foreign-body giant cell reaction that peaked at 8-12 d post-grafting, but neither acute inflammation nor evidence of immune stimulation were observed. Within 1 mo, many structural components of normal **skin** were reconstituted.

L9 ANSWER 42 OF 55 MEDLINE on STN
AN 1998437322 MEDLINE
TI In vitro reconstruction of a human capillary-like network in a tissue-engineered **skin** equivalent.
SO FASEB JOURNAL, **(1998 Oct)** 12 (13) 1331-40.
Journal code: 8804484. ISSN: 0892-6638.
AU Black A F; Berthod F; L'heureux N; Germain L; Auger F A
AB For patients with extensive burns, wound coverage with an autologous in vitro reconstructed **skin** made of both dermis and epidermis should be the best alternative to split-thickness **graft**. Unfortunately, various obstacles have delayed the widespread use of composite **skin** substitutes. Insufficient vascularization has been proposed as the most likely reason for their unreliable survival. Our purpose was to develop a vascular-like network inside tissue-engineered **skin** in order to improve **graft** vascularization. To reach this aim, we fabricated a **collagen** biopolymer in which three human cell types keratinocytes, dermal **fibroblasts**, and umbilical vein endothelial cells were cocultured. We demonstrated that the endothelialized **skin** equivalent (ESE) promoted spontaneous formation of capillary-like structures in a highly differentiated **extracellular matrix**. Immunohistochemical analysis and transmission electron microscopy of the ESE showed characteristics associated with the microvasculature in vivo (von Willebrand factor, Weibel-Palade bodies, basement membrane material, and intercellular junctions). We have developed the first endothelialized human tissue-engineered **skin** in which a network of capillary-like tubes is formed. The **transplantation** of this ESE on human should accelerate **graft** revascularization by inosculation of its preexisting capillary-like network with the patient's own blood vessels, as it is observed with autografts. In addition, the ESE turns out to be a promising in vitro angiogenesis model.